Remarks

The Office Action mailed January 5, 2006 has been received and reviewed. Claims 16, 17, 23, 27, 44, 46, 47, 51, 73, 74, 76, 78, 79, 80, 87, 108, 120 and 123 having been amended, claims 12, 22, 77, 93-95, 110-112, 121-122 and 124-126, 129-131 having been canceled without prejudice, the pending claims under consideration are claims 1-11, 13-21, 23-76, 78-92, 96-109, 113-120, 123, 127, and 128.

The amendment of claims 16, 17, 27, 44, 51, 87, and 108 is supported by the specification at, for instance, page 10, lines 17-25. The amendment of claims 76, 79, 80, 120, and 123 is supported by the specification at, for instance, page 11, line 9 through page 12, line 24. The amendment of claim 78 is supported by the specification at, for instance, page 12, lines 16-24.

Priority

The Examiner asserts the application contains disclosure not presented in the prior application, specifically the term "siRNA" in claims 77, 78, 122, 123, and 126, and that the application is thus a continuation-in-part. The Examiner has further stated that because of the newly added material, the application has priority only to its own filing date of February 5, 2004. Applicants respectfully traverse the characterization of the instant application as a continuation-in-part, and the assertion that the term siRNA is newly added material.

As stated in M.P.E.P. §2163.07, "mere rephrasing of a passage does not constitute new matter." The use of the term siRNA is a mere rephrasing of passages present throughout the specification. In the interests of furthering prosecution, claim 78 has been amended to delete the term "siRNA" and insert the phrase "double stranded RNA" therefor, and claims 77, 122, and 126 have been canceled. Claim 123 was incorrectly noted by the Examiner as reciting "siRNA." Claim 124 recites "siRNA," and has been canceled. Claims 79 and 80 also recite the term and have been amended to cancel "siRNA" and insert the phrase "double stranded RNA."

Accordingly, the Examiner is respectfully requested to withdraw the characterization of the instant application as a continuation-in-part.

Oath/Declarations

The Examiner has requested that a new oath or declaration be filed in accordance with 37 CFR 1.63(e) as a result of the current application being characterized as a continuation-in-part application, which Applicants respectfully traverse. Since the application is not continuation-in-part for the reasons discussed above, a new oath or declaration is not required.

Claim Objections

The Examiner has objected to claims 29 and 53 for reciting limitations from a non-elected invention. Claims 29 and 53 recited language directed to both elected and non-elected inventions. Claims 29 and 53 have now been amended to delete the language directed to an elected invention, and the deleted language is now present in claims 27 and 51. Accordingly, claims 29 and 53 are now directed to an non-elected invention, and have been marked in the section "Amendments to the Claims" as withdrawn. This renders the rejection moot.

Double Patenting Rejection

Claims 16, 17, 21, 22, 27, 29, 44-46, 51, 53, 87-90, 92, 98-101, 108 and 109 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 6, 18, 39 and 48 of co-pending Application No. 10/038,984. This rejection is respectfully traversed. However, upon an indication of otherwise allowable subject matter and in the event this rejection is maintained, Applicants will provide an appropriate response.

The 35 U.S.C. §112, Second Paragraph, Rejection

The Examiner rejected claims 22, 23, 46, and 47 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner rejected the claims for use of the phrase "such as." Applicants respectfully traverse the rejection. Nonetheless, in the interest of furthering prosecution of the application, claims 23, 46, and 47 have been amended to remove the phrase. Claim 22 has been canceled.

The Examiner has also rejected claims 73-75 as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regards as the invention. Specifically, the Examiner rejected the claims for reciting a compound according to a withdrawn claim. Applicants have amended claims 73 and 74 to recite the subject matter of claim 54, thereby removing reference to withdrawn claim 54.

For at least these reasons, reconsideration and withdrawal of the rejections of claims 23, 46, 47, and 73-75 under 35 U.S.C. §112, second paragraph, is respectfully requested.

The 35 U.S.C. §112, First Paragraph, Rejection

The Examiner rejected claims 1-13, 18-27, 29, 51, 53, 76-83, 87-92, 96-109, 113-126 and 128-131 under 35 U.S.C. §112, first paragraph, alleging that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Specifically, the Examiner has asserted that while the specification is enabling for a method of attenuating the expression of target genes in zebrafish cells in culture or zebrafish embryos, in avian neural crest tissue explant culture, and in rat cell culture, that it does not reasonably provide enablement for attenuating gene expression *in vivo* in any non-embryonic animal. The Examiner further asserts that the specification does not reasonably provide enablement for a method for treating a disease or infection in an organism. Claims 12, 22, 77, 121, 122, 124-126, and 129-131 have been canceled. This rejection is respectfully traversed.

The Examiner asserts that introduction of dsRNA targeted to a specific gene may result in attenuation of expression of the gene, but the degree of attenuation and the length of attenuation is not predictable (Office Action at page 7). For support, the Examiner cites Fire et al. (Nature, 391:806-811 (1998)) for indicating that introduction of dsRNA can result in a mosaic pattern of interference, and that the design of dsRNA is important as some designs are ineffective. Applicants note that the claims do not recite the degree of attenuation or the length of attenuation, thus these concerns do not render the invention unpredictable as claimed. Claims to the present invention specify that expression is attenuated, which is defined in the specification merely as "partial or complete inhibition of gene function," or that expression is inhibited. Thus any perceived unpredictability regarding degree of attenuation or length of attenuation is irrelevant with respect to evaluating enablement of the rejected claims.

Further, Applicants submit that the main observation of Fire et al. is that "[t]he phenotype produced by interference...was *extremely specific*. Progeny of injected animals exhibited behaviour that *precisely mimics* loss-of-function mutations..." (emphasis added) (Fire et al. at page 808, second column). Indeed, out of 19 dsRNA segments tested, the effects of all but one were limited to those expected from previously characterized null mutants, indicating remarkably reproducible specificity (Fire et al. at page 809, first column). The one exception was a protein with a highly conserved myosin-motor domain, and Applicants submit that one of ordinary skill in the art would suspect that dsRNA in that case would be expected to interfere with other related proteins. Fire et al. also describes dsRNA-mediated interference as "potent" and "specific" (Fire et al. at page 810, first column). Observations of Fire et al. concerning mosaicism do not argue against specificity, and the fact that dsRNA segments corresponding to various intron and promoter sequences did not produce detectable interference still did not rule out interference at the level of the gene (Fire et al. at page 809, second column).

The Examiner also cites Oates et al. (Developmental Biology, 2000) and Zhao et al (Developmental Biology, 2001) to support the existence of non-specific effects in zebrafish embryos. Other post-filing art supports the opposite conclusion. For instance, Kennerdell et al.

(Nat. Biotech., 18, 896-898 (2000), and Tavernarakis et al. (Nat. Genet., 24, 180-183 (2000)) demonstrate specific gene silencing in Drosophila and C. elegans, respectively. Further, in a review of silencing with double stranded RNA, these two documents are cited by Carthew (Curr Opin Cell Biol., 13, 244-248 (2001)) as "demonstrat[ing] that a transgene expressing an inverted repeat is a potent [post-transcriptional gene silencing] vector in animals. [Post-transcriptional gene silencing] can be induced in a cell-specific or a tissue-specific manner at different stages of the life cycle" (Carthew at page 247, bottom of column 2). Subsequent journal articles have confirmed that double stranded RNA is useful for the specific attenuation of genes in non-embryonic animals. The Examiner's reliance on the Oates et al. and Zhao et al. documents to suggest that the field of RNA interference is unpredictable is unfounded in view of the success of others in this field.

The Examiner asserts that specific gene inhibition by dsRNA in mammalian cells is unpredictable because longer dsRNA molecules have been observed to cause an induction of a PKR response, and that Applicants have not provided guidance regarding the use of shorter dsRNA. In support of this assertion, the Examiner cites Wianny et al. (Nature Cell Biology, 2000), which has reported that "it is possible that the early mouse embryo is incapable of an interferon response and that there may still be difficulties in using RNAi at later stages" (p. 73, under Discussion).

Applicants note that the claims do not recite language requiring the absence of a PKR response. These concerns do not render the invention unpredictable as claimed. Thus any perceived unpredictability based on induction of a PKR response is irrelevant with respect to evaluating enablement of the rejected claims.

Further, the interaction between the PKR response and RNAi is not yet well characterized, as indicated by Wianny's caveats that "it is possible" and "there may still be difficulties." This is hardly definitive language regarding an immune response to RNAi in mammalian cells, and this suggestion of possible problems is not sufficient to indicate that attenuation by RNAi in mammalian cells is unpredictable. Furthermore, Applicants have

demonstrated effective gene attenuation in mammalian cells (see Example III). This indicates Wianney's speculation "that there may still be difficulties in using RNAi at later stages" is not correct. Moreover, McCaffrey et al., (Nature, 418, 39 (2002), Soutschek et al. (Nature 432, 173 (2004)), and Caplen (Nature Medicine, 10(8), 775 (2004)) each demonstrate attenuation in adult mice, and none report difficulties related to induction of a PKR response. Thus, when comparing Wianney's speculative conclusions with the conclusive evidence provided by McCaffrey et al., Soutschek et al., and Caplen, the Examiner's assertion that "the post-filing art clearly suggests that administering dsRNA to vertebrate systems *in vivo*, to inhibit target genes is not a reproducible or predictable art" (Action at page 9) is unfounded.

The Examiner has also asserted that Applicants have not provided sufficient guidance on the use of shorter dsRNA to avoid the PKR response. Applicants respectfully disagree. Applicants have described the use of small amounts of dsRNA to avoid an immune response. See page 34, lines 26-28 which state that "the amount of double-stranded RNA that was used to generate the phenotypes is much less than is necessary to cause this interferon-mediated toxicity."

The Examiner asserts that the therapeutic use of nucleic acids was a highly unpredictable art at the time of the instant invention, and that the claimed invention encompasses methods of treating disease or infection in an organism. "All questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims." M.P.E.P.§2164.08. The claims as amended are not directed to treating any specific disease or specific infection, and do not specify that the resulting attenuation of gene expression has any therapeutic effect. It is not necessary to show a therapeutic effect for specific diseases if methods of treatment are not claimed.

The Examiner also asserts that Applicants have not provided sufficient guidance on selecting an appropriate route of administration or the amount of dsRNA required to effectively

attenuate gene expression. Applicants respectfully disagree, and point to page 13, line 29 to page 15, line 25, of the specification which provides numerous details on delivery of dsRNA. For example, the section on "Delivery of dsRNA to a cell" describes how to deliver dsRNA to an embryo, cell culture, and whole animals or plants. The specification also lists numerous methods, such as microinjection, particle bombardment, soaking the cell or organism in a solution containing the dsRNA, electroporation of cell membranes, etc. (see p. 14, lines 1-5). The dsRNA can also be delivered to a cell using a vector that encodes a dsRNA and causes the dsRNA to be transcribed within the cell (see p. 14, lines 21-27). Applicant further provides detailed examples of the use of microinjection in Example I and soaking in solution containing the dsRNA in Examples II and III. While cellular uptake was a concern early in the development of nucleotide-based treatment, researchers have come to understand that cells readily internalize nucleic acids and many such methods are well-established in the art.

Furthermore, as the claims merely recite language such as introducing the RNA to a cell or contacting an RNA with an organism, many of the traditional pharmacological concerns, such as how the dsRNA will be metabolized, and how it can be targeted to a particular location within an organism are simply not pertinent, as the dsRNA can be directly delivered to the site of interest by methods such as injection into a cavity. In the case of a DNA encoding the dsRNA, there is ample teaching in the art relating to delivery of such vectors into vertebrate cells. See, for example, U.S. Patent No. 5,580,859, entitled "Delivery of exogenous DNA sequences in a mammal," which teaches direct injection of a "naked" DNA expression vector into a mammal. The Examiner's statement that "the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that the gene is inhibited to a degree necessary to result in a therapeutic effect" (Office Action p. 10, first full paragraph) represents a misunderstanding of the scope of Applicants claims, which do not recite treating disease or infection in an organism.

The Examiner also notes that Coburn et al. (Journal of Antimicrobial Chemotherapy, 2003) have indicated that an impediment to using RNA interference therapeutically is that gene attenuation may be transient. Applicants again note that the present claims do not recite therapy,

nor do they recite that a particular duration of gene inhibition or attenuation is required. Transient gene attenuation would still provide attenuation. Thus, the argument that gene expression may be transient is not relevant to the enablement of the current claims, which do not require long-term gene attenuation.

The Examiner cites Agrawal et al (Molecular Medicine Today, 2000) as describing the technical difficulties encountered in delivering antisense nucleotides. However, antisense oligonucleotides can be successfully used in a variety of *in vivo* settings. Local delivery (e.g., intra opthalmically, inhalation, topically, etc.) generally provides the best results. However, the literature contains many examples of systemic delivery of antisense that have worked very well, and the majority of clinical trials currently ongoing with antisense oligonucleotides utilize systemic (primarily intravenous) delivery methods. Many reviews attest to the enormous progress made in the field of nucleotide delivery. For example, Wang et al. (Antisense and Nucleic Acid Drug Development, 13, 169 (2003)) state on page 169 that "With advances in oligonucleotide chemistry and progress made in formulation development, oligonucleotides are becoming widely acceptable drugs." The review by Wang et al. further describes how to specifically target oligonucleotides for the liver, and how to administer oligonucleotides by oral and colorectal administration, topical, and pulmonary delivery.

Regarding the assertion that the claims do not reasonably provide enablement for attenuating gene expression *in vivo* in any non-embryonic animal, it is Applicant's position that sufficient genes and species of cells are provided by the specification to support the claimed genus. The standard for such situations is set out in M.P.E.P. § 2164.02, where it states that "For a claimed genus, representative examples and a description of how to make and use the genus as a whole should be sufficient if a person skilled in the art would expect the claimed genus could be used in that manner without undue experimentation." It is submitted that Applicants have made an adequate showing of enablement in the specification for the claimed genus. Applicants have demonstrated, by working, representative examples, the specific attenuation of gene expression using double-stranded RNA (dsRNA) in the following diverse systems:

Cell/Organism/Tissue	Targeted Gene	Gene Function/Phenotype
zebrafish embryo	GFP	exogenous reporter gene (plasmid based)
zebrafish embryo	T gene	endogenous gene associated with midline development: *no tail* (*ntl*) phenotype
zebrafish embryo	Pax6.1	endogenous gene associated with head and eye development
zebrafish embryo	Nkx 2-7	endogenous gene associated with heart morphology and functioning
zebrafish embryo	T gene Pax6.1	see above (two genes targeted)
chick neural crest tissue	HirA	endogenous gene associated with persistent truncus arteriosus
rat cells	GFP	exogenous reporter gene (plasmid based)

Applicants direct the Examiner to M.P.E.P. § 2164.02 on Working Examples and a Claimed Genus, where it states that:

> For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art ... would expect the calimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

The chart helps illustrate that Applicants have shown successful gene silencing using dsRNA in a wide range of species and targeting a wide range of genes. Vertebrate cells as diverse as fish cells, mammalian cells and avian cells were silenced. And these are merely the vertebrate organisms for which examples are provided; the specification further describes the

target gene as being derived from any organism, with numerous examples of additional species being provided.

In addition to disclosing a large number of species, Applicants have used an organism that has been categorized as a model organism for vertebrates; namely, the zebrafish. The zebrafish has been used as a model for vertebrate development since at least the early 1990's. See for example "Zebrafish: genetic tools for studying vertebrate development", Driever et al., TIG, 10, 152-159 (1994). Use of the zebrafish includes the use of zebrafish as a model of human disease. See, for example, "Zebrafish: bridging the gap between development and disease" a review authored by Dodd et al. (Human Molecular Genetics, 9, 2443-2449 (2000)). Dodd et al. states, for example, that "the zebrafish (*Danio rerio*) represents an ideal genetic system for the study of both developmental biology and disease" (Dodd et al., p. 2443, first paragraph). As Applicants have demonstrated gene attenuation in a *model* organism, this should be given greater weight for the purpose of demonstrating gene attenuation in the genus modeled by that organism than would be provided by a typical species.

Applicants' specification provides further support for the predictability of gene attenuation. The phenotypes that were generated for each gene differed substantially from one another and were specifically and predictably related to the gene that was targeted (specification at page 34, line 32, bridging to page 35, line 2). For example, functionally attenuating expression of the zebrafish T gene resulted in a reproducible phenotype that mirrored that found of the *ntl* mutant where the same gene was altered by an insertional mutation (specification at page 31, line 16-18). Injection of control dsRNA at the same concentrations, on the other hand, did not cause a detectable deviation from the wild type expression levels or phenotype (specification at page 35, line 2-4). Furthermore, Applicants have shown that multiple genes can be targeted simultaneously (specification at, for example, page 35, lines 8-9), further evidencing the robustness of the method of the invention. Applicants have also shown that the timing and/or amount of the dsRNA injected can predictably generate partial phenotypes of varying severity.

Finally, Applicants note that the presumption is that an application is enabled, and that this is overcome only if the Examiner can show that undue experimentation is necessary to use the invention as claimed. Furthermore, the mere fact that experimentation may be involved, and even be complex, does not necessarily make the experimentation undue. Applicants do not believe undue experimentation would be necessary to practice the invention as claimed. It is well-established that some experimentation is often to be expected in unpredictable technologies, such as molecular biology. The question is whether the amount of experimentation needed to practice the invention, as claimed, is undue. This question is answered more readily if the method of the invention is broken down into separate steps. For the first step, to attenuate the expression of a target gene in a vertebrate cell, the nucleotide sequence of the gene can obtained either from a database or from routine procedures used to determine the sequence of a gene. RNA capable of hybridizing to the target gene is then synthesized, again using routine methods known to those skilled in the art. Finally, the dsRNA is supplied to a vertebrate cell through the delivery methods discussed above, which are again routine and known to those skilled in the art.

Further, subsequent publications have confirmed that double stranded RNA is useful for gene expression *in vivo* in any non-embryonic vertebrate animal. For instance, Sorensen et al. (J. Mol. Biol., 327, 761-766 (2003)) show gene silencing by systemic delivery of double stranded RNA to adult mice resulted in specific inhibition of expression of exogenous and endogenous genes. McCaffrey et al. (Nature, 418, 39 (2002)) show systemic delivery of double stranded RNA to adult mice resulted in specific double stranded RNA mediated inhibition of exogenous genes. Soutschek et al. (Nature 432, 173 (2004)) show gene silencing by systemic delivery of double stranded RNA to adult mice resulted in specific inhibition of expression of an endogenous gene. Further, even though these documents are post-filing art, the skilled person in possession of the present application could practice these methods by relying on the teachings of the present application and the knowledge generally available in the art. Thus, each of these demonstrate that the present application enables the attenuation of gene expression *in vivo* in any non-embryonic vertebrate animal.

For at least these reasons it is respectfully submitted that the present invention is fully enabled. Reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph, is respectfully requested.

The 35 U.S.C. §102 Rejection

The Examiner rejected claims 1-5, 7, 9-13, 16-27, 29, 44-51, 53, 87-92, 96-101, 103, 104, 108, 109 and 113-116 under 35 U.S.C. §102(b) as being anticipated by Agrawal et al. (WO 94/01550), and claims 1, 2, 6-11, 16-19, 21, 23, 24, 44, 45, 47, 48, 87-92 and 99-102 as being anticipated by Cameron et al. (Prov. Natl. Acad. Sci. USA 1989, Vol. 86, pages 9139-9143).

The Examiner rejected claims 120, 127-129 and 131 under 35 U.S.C. §102(e) as being anticipated by Cowsert (U.S. Patent No. 5,945,290), claims 1-13, 16-27, 29, 44-51, 53 and 87-119 as being anticipated by Fire et al. (U.S. Patent No. 6,506,559), claims 1, 7-10, 16-18, 22, 23, 76, 80-82, 87-89, 92 and 107 as being anticipated by Graham (U.S. Patent No. 6,573,099), and claims 120-125 and 127 as being anticipated by Brown et al. (U.S. 2004/0029275).

To anticipate a claim, a single source must contain all of the elements of the claim. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986); *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1574, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984); *In re Marshall*, 578 F.2d 301, 304, 198 U.S.P.Q. 344, 346 (C.C.P.A. 1978). Missing elements may not be supplied by the knowledge of one skilled in the art or the disclosure of another reference. See *Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716, 223 U.S.P.Q. 1264, 1271 (Fed. Cir. 1984).

Rejection of Claims under 35 USC §102(b)

The Examiner rejected claims 1-5, 7, 9-13, 16-27, 29, 44-51, 53, 87-92, 96-101, 103, 104, 108, 109 and 113-116 under 35 U.S.C. §102(b) as being anticipated by Agrawal et al. (WO 94/01550). Claims 12 and 22 have been canceled. Applicants respectfully traverse the rejection.

Agrawal et al. disclose oligonucleotides and methods for using oligonucleotides. Agrawal et al. disclose several types of oligonucleotides, but when considered in its entirety, it teaches methods of using only one type of oligonucleotide. This is a relevant distinction, as the pending claims are directed to methods of use.

Agrawal et al. teach oligonucleotides can be polymers of ribonucleotides, deoxyribonucleotides, or both (page 8, lines 6-21). The oligonucleotides have two regions, a target hybridizing region and a self-complementary region (page 8, line 22 though page 10, line 13). Agrawal et al. further teach oligonucleotides having a structure that activates RNase H. Several preferred embodiments of this aspect of Agrawal's invention are described at page 13, line 25 through page 14, line 10, but the inventors note "[t]hese preferred embodiments all provide for the activation of RNase H, as long as four or more contiguous deoxyribonucleotide phosphodiesters, phosphorothioates, or phosphorodithioates are present" (page 14, lines 5-8).

Agrawal et al. teach several advantages to the oligonucleotides disclosed therein, including "the enzymatic stability afforded by the base-paired structures involving the self-complementary sequences allows the use of oligonucleotide phosphodiesters, which otherwise are rapidly degraded. This provides the advantages of increased duplex stability and RNase H activation . . . . " (page 19, line 29 through page 20, line 3).

Agrawal et al. also teach methods of using the oligonucleotides, and state that "[o]ligonucleotides according to the invention form stable hybrids with target sequences under physiological conditions, activate RNase H and produce only nucleosides as degradation products" (page 5, lines 9-12). The inventors further characterize their invention by stating "[t]his results in oligonucleotides that activate RNase H, an important feature for the antisense therapeutic compound" (page 5, line 36 through page 6, line 2, emphasis added).

Thus, Agrawal et al. teaches methods of using oligonucleotides, but in view of the teachings of Agrawal et al., including the teachings at page 19, line 29 through page 20, line 3, page 5, lines 9-12, and page 5, line 36 through page 6, line 2, the oligonucleotides to be used in the methods are those that activate RNase H, and such oligonucleotides include "four or more

contiguous deoxyribonucleotide phosphodiesters, phosphorothioates, or phosphorodithioates" (page 14, lines 5-8).

In contrast, the rejected claims recite methods involving the use of an RNA. Specifically, the rejected claims recite "a method . . . comprising: introducing into the cell an RNA comprising a double stranded structure" (independent claim 1), "a method . . . comprising introducing double stranded RNA (dsRNA) into the cells" (independent claim 16), "a method . . . comprising introducing at least one double stranded RNA (dsRNA) into the cells" (independent claim 17), "a method . . . comprising introducing at least one double stranded RNA (dsRNA) into the mammalian cell" (independent claim 18), "a method . . . comprising introducing into the cell a hairpin ribonucleic acid" (independent claims 27 and 51), "a method . . . comprising introducing into the cell a double stranded RNA (dsRNA)" (independent claim 44), "a method . . . comprising introduction of a ribonucleic acid (RNA) into the cell" (independent claim 87), and "a method . . . comprising . . . contacting a ribonucleic acid (RNA) with the organism" (independent claim 108).

Agrawal et al. do not teach methods directed to introducing an RNA into a cell or contacting a cell with an RNA. Since Agrawal et al. do not teach such a use, Agrawal et al. cannot anticipate the rejected claims.

For at least these reasons, reconsideration and withdrawal of the rejection of claims 1-5, 7, 9-13, 16-27, 29, 44-51, 53, 87-92, 96-101, 103, 104, 108, 109 and 113-116 under 35 U.S.C. §102(b) as being anticipated by Agrawal et al. (WO 94/01550) is respectfully requested.

The Examiner rejected claims 1, 2, 6-11, 16-19, 21, 23, 24, 44, 45, 47, 48, 87-92 and 99-102 under 35 U.S.C. §102(b) as being anticipated by Cameron et al. (Prov. Natl. Acad. Sci. USA 1989, Vol. 86, pages 9139-9143). More specifically, the Examiner asserts that Cameron et al. disclose specific gene suppression by engineered ribozymes in monkey cells. The Examiner further asserts that the ribozyme nucleic acids disclosed by Cameron et al. are double stranded, referring to Figure 1A of Cameron et al. This rejection is respectfully traversed.

Cameron et al. disclose specific gene expression by engineered ribozymes in monkey cells. The ribozymes are double stranded, and an example of such a ribozyme is shown in Figure 1a of Cameron et al. The double stranded region of the ribozyme is four nucleotides in length (3'-CAGG, which hybridizes with 5'-GUCC), and corresponds to the stem-loop structure of the ribozyme . The other double stranded region present in Figure 1a corresponds to a region of complementarity between the ribozyme and the target gene. The ribozyme itself is not double stranded in this region, it is single stranded.

In contrast, the rejected claims recite "an RNA comprising a double stranded structure having a nucleotide sequence which is substantially identical to at least a part of the target gene" (independent claim 1), "double stranded RNA (dsRNA) . . . wherein the dsRNA comprises a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence of the target gene" (independent claims 16-18, and 44), "ribonucleic acid (RNA) . . . wherein the RNA comprises a double-stranded structure with an identical nucleotide sequence as compared to a portion of the target gene" (independent claim 87). Cameron et al. do not teach an RNA molecule having a double stranded structure that includes a nucleotide sequence that is identical to, or hybridizes with, a target gene. Since Cameron et al. do not teach such an RNA molecule, Cameron et al. cannot anticipate the rejected claims.

For at least these reasons, reconsideration and withdrawal of the rejection of claims 1, 2, 6-11, 16-19, 21, 23, 24, 44, 45, 47, 48, 87-92 and 99-102 under 35 U.S.C. §102(b) as being anticipated by Cameron et al. (Prov. Natl. Acad. Sci. USA 1989, Vol. 86, pages 9139-9143) is respectfully requested.

Rejection of Claims under 35 USC §102(e)

The Examiner rejected claims 120, 127-129 and 131 under 35 U.S.C. §102(e) as being anticipated by Cowsert (U.S. Patent No. 5,945,290). More specifically, the Examiner has asserted that Cowsert discloses that RhoA expression can be inhibited by administration of

multiple antisense oligonucleotides directed to RhoA. Claims 129 and 131 have been canceled. This rejection is respectfully traversed.

Cowsert discloses antisense compounds and compositions for modulating the expression of RhoA. The antisense compounds, typically referred to throughout Cowsert as oligonucleotides, specifically hybridize with one or more nucleic acids encoding RhoA (col. 2, lines 46-56). Oligonucleotides can be RNA or DNA (col. 5, lines 20-22). Cowsert does not appear to teach double stranded RNA molecules.

In contrast, independent claim 120 recites "delivering to the cell a combination of two or more double stranded RNA molecules." Since Cowsert does not appear to teach a double stranded RNA molecule, Cowsert cannot anticipate the rejected claims.

For at least these reasons, reconsideration and withdrawal of the rejection of claims 120, 127-129 and 131 under 35 U.S.C. §102(e) as being anticipated by Cowsert (U.S. Patent No. 5,945,290) is respectfully requested.

The Examiner rejected claims 1-13, 16-27, 29, 44-51, 53 and 87-119 under 35 U.S.C. §102(e) as being anticipated by Fire et al. (U.S. Patent No. 6,506,559). Claims 12 and 22 have been canceled. Applicants respectfully traverse the rejection. However, in the interest of furthering prosecution, claims 16, 17, 27, 44, 51, 87, and 108 have been amended to recite vertebrate cells.

To constitute an anticipatory reference, the prior art must contain an enabling disclosure. Chester v. Miller, 906 F.2d at 1576 n.2, 15 U.S.P.Q.2d at 1336 n.2 (Fed. Cir. 1990). Applicants respectfully disagree that Fire et al. provides an enabling disclosure for mammalian cells (independent claims 1 and 18) or vertebrate cells (independent claims 16, 17, 27, 44, 51, 87, or 108). Mere passing reference to vertebrate or mammalian animals, as provided in column 8, lines 35-51 of Fire et al., does not enable the attenuation of gene expression in vertebrate or mammalian cells, any more than Fire et al.'s listing of over 100 types of cancer on column 10, line 28 to column 11, line 4 provides an enabling disclosure for cancer treatment. The only detailed description of work done by Fire et al. was in *C. elegans*. This does not provide an

enabling disclosure for vertebrates or mammals. Not only is *C. elegans* an invertebrate, but it is a primitive and simple invertebrate. It is only 1 mm long, includes only 959 somatic cells, and is often handled as a microorganism; for example, it is usually grown on petri plates seeded with bacteria. The description of dsRNA administration to this single, simple, invertebrate organism does not provide an enabling disclosure for the claimed methods in vertebrate and mammalian cells.

For at least these reasons, reconsideration and withdrawal of the rejection of claims 1-13, 16-27, 29, 44-51, 53 and 87-119 under 35 U.S.C. §102(e) as being anticipated by Fire et al. (U.S. Patent No. 6,506,559) is respectfully requested.

The Examiner rejected claims 1, 7-10, 16-18, 22, 23, 76, 80-82, 87-89, 92 and 107 under 35 U.S.C. §102(e) as being anticipated by Graham (U.S. Patent No. 6,573,099). More specifically, the Examiner asserts that Graham et al discloses genetic constructs containing multiple copies of genes, and claims a method of reducing expression of a target gene in an animal cell using an expression construct containing two or more copies of a structural gene. Claim 22 has been canceled. Applicants respectfully traverse the rejection.

Graham does not teach each element of the rejected claims. Moreover, the disclosure of Graham does not satisfy the 35 U.S.C. §112 enablement requirement. "The disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation." M.P.E.P §2121.01. "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." M.P.E.P. §2164.01. Thus, to determine if a specification is enabling, the examiner should consider the experiments used in the specification as filed as well as what was known to one of skill in the art at the time of filing.

Graham discloses no working examples and no prophetic examples regarding methods for delaying or repressing the expression of a target gene in, for instance, a mammalian cell,

cultured vertebrate cells, or a vertebrate cell. Graham only sets forth methods for making a multitude of different plasmids, and many of these are prophetic. Thus, clearly the examples were very narrow compared to the breadth of the disclosure.

Furthermore, with respect to what was known to one of skill in the art at the time Graham was filed, it would have been unclear to the skilled person whether double stranded RNA would form in a cell after expression in a cell. For instance, it would have been unclear to the skilled person whether molecules in a cell, such as proteins, would bind individual single stranded RNAs and prevent hybridization. It would have been unclear to the skilled person if the conditions inside a cell, such as temperature and salt concentration and concentration of single stranded RNAs, would prevent formation of double stranded RNA. It would also have been unclear to the skilled person if a hairpin double stranded RNA would be produced in a cell from plasmids disclosed in Graham. Furthermore, the skilled person was aware of only very little at the time Graham was filed. For instance, the first Fire document (Nature, 391:806-811 (1998)) was published in February, 1998, 4 months before Graham was filed. In a review published in the same issue of Nature as the Fire document, Wagner (Nature, 391:744-745 (1998)) considers the Fire document to represent "a remarkable and surprising technique for inhibiting gene function in *C. elegans*" and goes on to question whether "a similar phenomenon exist in other organisms."

Graham at most represents a research plan that sets out plasmids representing the confusing state of art in the field of co-supression at the time it was filed. As Graham states at column 1, lines 29-48, attempts were being made to regulate gene expression in cells, but the attempts were largely unsuccessful, the efficiency of the methods were low, and the results variable and unpredictable. The teachings of Graham do nothing to change the state of the art as described by Graham.

For at least these reasons, reconsideration and withdrawal of the rejection of claims 1, 7-10, 16-18, 22, 23, 76, 80-82, 87-89, 92 and 107 under 35 U.S.C. §102(e) as being anticipated by Graham (U.S. Patent No. 6,573,099) is respectfully requested.

The Examiner rejected claims 120-125 and 127 under 35 U.S.C. §102(e) as being anticipated by Brown et al. (U.S. 2004/0029275). Applicants respectfully disagree that Brown et al. constitutes a prior art reference under 35 U.S.C. §102(e). As described above, Applicants disagree that use of the term "siRNA" provides new material, and have amended the claims to no longer recite "siRNA." As Brown et al. has a filing date of November 15, 2002, it is not prior art. Accordingly, Applicants respectfully request that the rejection of claims 120-125 and 127 under 35 U.S.C. §102(e) as being anticipated by Brown et al. (U.S. 2004/0029275) be withdrawn.

The 35 U.S.C. §103 Rejection

The Examiner rejected claims 120-129 and 131 under 35 U.S.C. §103(a) as being unpatentable over Cowsert as applied to claims 120, 127-129 and 131 above, and further in view of Brown et al. Claims 121, 122, 124-126, 129, and 131 have been canceled. This rejection is respectfully traversed.

As discussed above, Cowsert discloses antisense compounds and compositions for modulating the expression of RhoA. The antisense compounds, typically referred to throughout Cowsert as oligonucleotides, specifically hybridize with one or more nucleic acids encoding RhoA (col. 2, lines 46-56). Oligonucleotides can be RNA or DNA (col. 5, lines 20-22). Cowsert does not appear to teach double stranded RNA molecules. Also as discussed above, Brown is not prior art, and therefore cannot be used to supplement the deficiencies of Cowsert et al.

The Examiner has not presented any evidence that the skilled person would have found the claimed invention to have been obvious in light of the teachings of Cowsert. Accordingly, the Examiner has failed to represent a prima facie case of obviousness. Reconsideration and withdrawal of this rejection is respectfully requested.

Summary

It is respectfully submitted that the pending claims are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

CERTIFICATE UNDER 37 C.F.R. 1.10:

The undersigned hereby certifies that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated below and is addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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